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REVIEW ARTICLE



## Ethnopharmacology<sup>†</sup>

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### ABSTRACT

**Background:** Ethnopharmacology relates to the study of substances used medicinally by different ethnic or cultural groups or handling of, drugs-based ethnicity or pharmacogenetics.

**Aims:** To review the key aspects of ethnopharmacology.

**Method:** This lecture gives an overview of the relationship between geography, culture, pharmacogenomics and prescribing.

**Results:** Although the majority of antipsychotics, antidepressants and mood-stabilisers are widely and cheaply available in generic forms, prescription rates can vary. Clozapine is one such example with prescribing-rates ranging from less than 10 patients per 100,000 people to nearly 180 patients/100,000 people. Pharmacogenetic studies of antipsychotics and antidepressants concern gene polymorphisms that may affect both, pharmacodynamic or pharmacokinetic properties. Considerable genetic and ethnic variability has been seen for the P450 microsomal enzymes CYP 2D6 and 1A2.

**Conclusions:** With accelerated global mobility and increased understanding of medicinal substances at molecular level, understanding of ethnopharmacology will become increasingly important in routine clinical practice.

### KEYWORDS

Ethnopharmacology;  
pharmacogenomics; CYP;  
antipsychotics;  
antidepressants

## Introduction

The subject of ethnopharmacology encompasses two distinct areas of study: substances used medicinally by different ethnic or cultural groups (e.g. folk remedies); and differences in response to, or handling of, drugs-based ethnicity or pharmacogenetics. Both aspects share the same promise of step-change advances in pharmacotherapy but neither has yet delivered on this expectation.

## Ethnopharmacology – geography, culture and prescribing

The treatment of psychiatric disorders is perhaps somewhat uniform around the world. The majority of antipsychotics, antidepressants and mood-stabilisers have long since lost any patent protection and are widely and cheaply available in generic forms. Uniform availability does not, however, always assure the uniform prescription rates. A good example here is the use of clozapine. Christian Bachmann and colleagues collected data on clozapine prescribing in 17 countries [1]. The rate of prescribing ranged from less than 10 patients per 100,000 people to nearly 180/100,000 people. More striking than this variation was the varied pattern of clozapine prescribing in each country. Lithuania, the highest user of clozapine, showed perhaps the expected pattern: minimal use in those aged under 19 and over 80 years and

peak used in those in middle age. Prescribing in Japan was the lowest rate reported and was concentrated in patients aged 20–49 years. In marked contrast, prescribing in Columbia was concentrated almost entirely in those older than 80 years of age. The United States and Sweden showed usage in a similar pattern of Lithuania but with something of a right-shift because of higher rates of prescribing in the 50+ group.

The reasons for the wide differences in overall use and in patterns of use are far from clear. One obvious influence is the time of introduction of clozapine. For example, clozapine has been available in Japan for only a few years, so one would perhaps not expect widespread prescribing. Another factor is the difference in regulations relating to clozapine prescribing. A study conducted in 2016 [2], found significant variation in regulations for clozapine use across nine countries. Differences were found in licensed indications, frequency of blood monitoring, thresholds for stopping clozapine, definition of treatment resistance and even licensed dose range. Tacit recognition of the power of regulations to restrain clozapine use is provided by the introduction of the REMS (Risk Evaluation and Mitigation Strategy) in the USA – one of the lowest uses of clozapine in the Bachmann study. This scheme replaced all the individual patient registries in an attempt to assure safe use and promote wider use of clozapine [3].

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**Table 1.** Ethnic variation of the cytochrome P450 CYP 2D6 [14].

Ethnicity	PM	U-RM
Caucasian	6-10%	1-10%
Asian	0-2%	1%
African	5%	5-29%
Middle Eastern	1-2%	21%
Amerindian	2.2-2.4%	0%

McGraw and Waller 2012 (and others)

Apart from clozapine use, perhaps the best example of cultural variation in psychotropic use is of the St John's Wort [4,5] – a natural product of variable content used extensively in Germany and northern Europe but much less so elsewhere.

### Ethnopharmacology – pharmacogenetics

The concept of prescribing according to pharmacogenetics characteristics offers the prospect of improved efficacy and tolerability as a result of targeted interventions. Efforts have been made to identify the genetic factors associated with treatment response. This would allow specific drugs to be used in specific patients with a high likelihood of response. Where variation in response was found to be linked to receptor genotype, this would provide insight into the mode of action of the drug.

A review of studies examining clozapine response [6] identified numerous gene polymorphisms associated with good outcome. These included gene polymorphisms to D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors as well as those for 5HT<sub>2A</sub>, 5HT<sub>2C</sub>, 5HT<sub>6</sub> receptors and numerous glutamine transporter genes. The high number of statistically significant associations may owe as much to the repeated application of statistical tests as to true associations. The same is true for clozapine and agranulocytosis where at least six gene polymorphisms were identified as being linked to this adverse effect. And likewise, olanzapine response where gene polymorphism associations were reported for six genes (COMT, D<sub>3</sub> (2 polymorphisms), GRM3, 5HTT and MDR1).

The associations discovered so far have not as yet led to any change in the way clozapine or olanzapine are prescribed. The most startling differences in outcome according to genotype have been identified for the antipsychotic iloperidone. In a controlled study versus ziprasidone [7], patients were grouped according to the response to iloperidone and combinations of six marker genes. The group with the most favourable combination showed a response rate of 75%, those with the least favourable just over 10%. The same group [8] identified different genetic markers linked to iloperidone's effect on the QT interval. Other studies have found 13 polymorphisms of a gene linked to antipsychotic-associated weight gain [9].

In the most recent study [10], 2413 patients were randomly assigned an individual antipsychotic treatment and genome-wide associations were investigated. Five new gene loci were found to be linked to response, most of these being related to synaptic function. Nonetheless, the authors

of this study declared that their results had 'scant clinical utility' at least at present.

Attempts to discover genetic predictors of response to antidepressants have also been somewhat unproductive. Combined results from three studies (GENDEP, MARS and STAR\*D) were unable to show any predictive associations despite testing 1.2 million polymorphisms [11]. A further attempt to pull out something from these expensive and publicly funded trials [12] found little of note. Other workers suggest that 5HT<sub>2A</sub> receptor polymorphisms predict response to antidepressants [13].

A somewhat better developed aspect of pharmacogenetics is the study of the role of genetic variation in cytochrome function and its relationship to drug dosing and response [1–3]. Cytochromes and other phase I enzymes (alcohol dehydrogenase, aldehyde dehydrogenase, etc.) are usually found in the liver but also function in the gut wall and in the brain. The speed with which cytochrome enzymes catalyse reactions (and therefore rate of metabolism) is genetically determined. In poor metabolisers, drug metabolism is slowed down. Thus, poor metabolizers are more prone to adverse effects. Slower conversion to active metabolites can potentially also lower efficacy. In rapid metabolisers, drug metabolism is accelerated. Thus, drug elimination rates are increased, and rapid metabolizers may need higher doses to achieve efficacy. The table below shows the relative frequency of poor and ultra-rapid metabolisers by CYP2D6 in different ethnic groups [14] (Table 1). As most SSRIs and many antipsychotics, including risperidone and aripiprazole are substrates of CYP 2D6, a higher proportion of patients from African or Middle Eastern background may experience lower drug efficacy and require dose increases.

Another example is CYP 1A2, implicated for instance in the metabolism of clozapine and olanzapine. Asian and African populations may experience lower CYP 1A2 activity than Caucasians [14,15]. For instance, one study showed that Swedes had 1.5 times higher CYP 1A2 activity than Koreans [15,16]. Thus, a higher proportion of patients from Asian and African background may have an increased risk of adverse effects and require dose decreases. The rate of CYP 1A2 reduction may also be influenced by other inducers, such as tobacco smoke. However, 35–85% of the CYP 1A2 response variability may be due to genetic factors [15,17].

### Conclusions

With accelerated global mobility and increased understanding of medicinal substances at molecular level, understanding of ethnopharmacology will become increasingly important in routine clinical practice. Ethnic variability of pharmacogenetics factors should be considered as a potential cause for unexpected lack of effectiveness or increased experience of adverse effects. Testing for genotype or phenotype would inform drug choice and drug dose both for CYP2D6 and CYP1A substrates and other substances subject to genetic variability.

## Disclosure statement

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